Exhibit 8

Specific Causation Expert Report: David Downs

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Cancer, Urologic Oncology, and the *British Journal of Urology International*. I am involved with the American Urologic Association Guidelines panel for evaluation of hematuria and muscle invasive bladder cancer.

I have served as the Chair of the AUA core curriculum. I am on the core committee for the international bladder cancer group. I am on the external advisory board for a large NIH trial (CISTO) and the Prevail Steering Committee. I have also served on the American Urological Association Education Council. I serve on the Scientific Advisory Board of the Bladder Cancer Advocacy Network.

I currently hold a position as co-chair of the Harold C. Simmons Comprehensive Cancer Center disease-oriented team, focused on urologic cancers. I am a member of UT Southwestern's Clinical Research Planning Group and the Tissue Bank Steering Committee and Cancer Committee. I have presented my work and lead panel discussions at medical conferences around the world and belong to numerous professional organizations, including the American Urological Association, the Society of Urologic Oncology, and the Bladder Cancer Advocacy Network.

III. Summary of Opinions

Trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, 1,2-dichloroethylene (DCE) and vinyl chloride, are known to cause kidney cancer. The data supporting this opinion is based on multiple studies evaluating the causal relationship and mechanistic effect of the toxins in the water at Camp Lejeune on cell lines and animal models.

The International Agency for Research on Cancer (IARC) classified TCE as a Group 1 carcinogen.[1] The ATSDR report itself states that there is sufficient evidence for causation for TCE causing kidney cancer.[2] There are multiple other governmental agencies that have found a causal relationship between TCE and kidney cancer, including EPA's most recent 2024 rule making wherein EPA banned the use of TCE.[3] The evidence is clear that TCE causes kidney cancer and in Mr. Downs' case, it is **more likely than not t**hat the TCE in the water at Camp Lejeune caused his kidney cancer. The other toxins in the water, namely PCE and VC, are also known to be carcinogenic[1,4] and also likely contributed to the kidney cancer in lesser amounts than the TCE.

[redacted]

Based on his overall history, David Downs' exposure to the water at Camp Lejeune was more likely than not the cause of his kidney cancer, necessarily exceeding the standard at issue in this case, an "at least as likely as not" standard.

All my opinions are expressed to a reasonable degree of scientific/medical certainty.

IV. Records Reviewed

During this evaluation, I reviewed and relied on the documents found in the materials considered list attached to this report.

V. Methodology

I have been asked to determine whether David Downs' exposure to the contaminated water at Camp Lejeune was "at least as likely as not" a cause of his kidney cancer. In order to provide this opinion, I conducted a search of the published scientific literature using the National Library of Medicine's PUBMED data base and reviewed the relevant peer-reviewed articles resulting from the search as well as other relevant reports such as the "ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases".[2] Reviews of epidemiological studies involving TCE and/or PCE exposure have been conducted by EPA (2011),[5] IARC (2014)[1] and NTP (2015).[6] In addition, I reviewed the meta-analyses that have recently been conducted by NCI researchers,[7,8,9] and an IARC workgroup for TCE and kidney cancer, hematopoietic cancers and liver cancer, and PCE and bladder cancer.[1] ATSDR utilized these reviews and meta-analyses to identify epidemiological studies for TCE and PCE. I also reviewed other relevant studies regarding TCE and kidney cancer risk such as Hansen 2013, Vlaanderen 2013, Christensen 2013, Silver 2014, Buhagen 2016, Moore 2010, and Raaschou-Nielsen 2003.[10,11,12,13,14,15,16]

I examined the risk factors for kidney cancer and contemporary evidence on kidney cancer prevention and screening. I assessed this by evaluating English-language meta-analyses and/or prospective randomized controlled trials published since January 2017. Where these were unavailable, original studies and previous systematic or narrative reviews were included in the evidence synthesis.

In evaluating for causation, I reviewed the medical records for Mr. Downs and his deposition to determine his risk factors for kidney cancer as well as his diagnosis and outcomes of his disease.

To determine the impact of exposure to the water at Camp Lejeune and Mr. Downs' kidney cancer diagnosis, I used, in part, the Bradford Hill criteria. These are scientifically valid criteria that have been used to assess causation. In 1965 Bradford Hill concisely described these criteria in evaluating aspects of an association to especially consider before deciding that the most likely interpretation of the evidence is causation. The nine criteria to consider include the following:

1. Strength of the association
2. Consistency of the observed association.
3. Specificity of the association
4. Temporality, i.e., the temporal relation of the exposure to the observed event
5. Biological gradient, i.e., one which can reveal a biological gradient, or dose response curve

6. Plausibility, i.e., if the causation we suspect is biologically plausible.
7. Coherence: should not seriously conflict with the generally known facts of the the natural history and biology of the disease
8. Experiment, i.e., occasionally it is possible to appeal to experimental, or semi-experimental, evidence. For example, because of an observed association some preventive action is taken. Does it in fact prevent?
9. Analogy, i.e., in some circumstances it would be fair to judge by analogy.[17]

As Bradford Hill noted when he proposed these criteria, none of his nine points to consider can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. As noted in his paper, what the criteria can do, with greater or lesser strength, is to help inform the answer to the fundamental question – (1) is there any other way of explaining the set of facts available, and (2) is there any other answer equally, or more, likely than cause effect?

In addition, Bradford Hill notes in his address that "No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."[17]

While I used the Bradford Hill criteria, in part, the conclusions in this report incorporate the patient's clinical factors as well as the weight of evidence related to carcinogens.

This methodology is consistent with how I perform this type of analysis and how reasonable physicians in my field apply the same and similar standards.

VI. Classification of Evidence

The Agency for Toxic Substances and Disease Registry (ATSDR) report identified that several classification systems have been developed to reflect the strength of the evidence for a causal relationship between an exposure and a particular health effect.[2] These include the IARC, EPA and NTP findings.[2] The ATSDR's assessment was primarily based on the epidemiological evidence. In their Assessment of the Evidence (2017), they used the classification scheme recommended by an IOM panel that reviewed the VA's presumptive disability decision-making process for veterans.[2,18] "This scheme makes clear when the evidence for causality is 'at least as likely as not' or at the level of 'equipoise and above.' ATSDR adopted this scheme because of its focus on the epidemiological evidence for causation (i.e., there is no category for evidence of a statistical association). Additionally, the scheme is one that is already in use by the U.S. Department of Veterans Affairs (VA) in its decision-making concerning compensation for service-related disability compensation claims."[2] The classification scheme uses four categories:

1. Sufficient: the evidence is sufficient to conclude that a causal relationship exists.

2. Equipoise and Above: the evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.

VIII. The Levels of the Chemicals in the Water at Camp Lejeune Were at Sufficient Levels to Cause Mr. Downs' Kidney Cancer

There were several epidemiological studies designed to study the exact exposure at issue in this case. The ATSDR and Dr. Bove et al. conducted a series of studies relating to Camp Lejeune and several diseases.

The Bove 2014a study compared the cancer mortality for marines and navy personnel stationed at Camp Lejeune to those stationed at Camp Pendleton.[19] This design was chosen since Camp Lejeune and Camp Pendleton are both military bases that are likely to be similar populations.[19] Camp Pendleton was chosen as a comparison cohort because it was assumed that people at Camp Lejeune were exposed to toxic chemicals while people at Camp Pendleton were not during the relevant period.[19] The study calculated that on average, an individual in the Camp Lejeune cohort resided at the base for approximately18 months.[19]

David Downs was at Camp Lejeune for a longer amount of time, approximately 589 days over a 20-month period. During that time, he had exposures to 43 microgram/liter-months of TCE, 939 microgram/liter-months of PCE and 122 microgram/liter-months of vinyl chloride at Tarawa Terrace and 282 microgram/liter-months of TCE at Hadnot Point.

When compared to Camp Pendleton, marines at Camp Lejeune demonstrated a hazard ratio of 1.35 (0.84-2.16) of dying from kidney cancer.[19] This indicates that by virtue of being stationed at Camp Lejeune (rather than Camp Pendleton) the kidney-cancer risk increased by 35%. The authors also analyzed the kidney cancer risk for different cumulative exposures to the relevant chemicals.[19] So, for example, if a marine was on base for one month during a time period when the concentration of TCE was 100 micrograms per liter, his cumulative exposure would have been 100 micrograms/liter-months. If he was on base for two months during that time period, his cumulative exposure would have been 200 micrograms/liter-months.

In the Bove 2014a study, for TCE, low exposure was defined as between 1 and 3,100 micrograms/liter-months.[19] Medium exposure was defined as between 3,100 and 7,700 micrograms/liter-months.[19] High exposure was defined as between 7,700 and 39,745 micrograms/liter-months.[19] As such, Mr. Downs met criteria for low exposure to TCE. This was associated with a HR of 1.54.[19]

For all of the chemicals combined (which the authors called TVOC, or total volatile organic compounds), low exposure was defined as between 1 and 4,600 micrograms/liter-months.[19] Medium exposure was defined as between 4,600 and 12,250 micrograms/liter-months.[19] High exposure was defined as between 12,250 and 64,016 micrograms/liter-months.[19] As such, Mr. Downs met criteria for low exposure to TVOC. This was associated with a HR of 1.42.[19]

In the Bove 2014a study, for PCE, low exposure was defined as between 1 and 155 micrograms/liter-months.[19] Medium exposure was defined as between 155 - 380 micrograms/liter-months.[19] High exposure was defined as between 380-8585 micrograms/liter-months.[19] As such, Mr. Downs met criteria for high exposure to PCE. This was associated with a HR of 1.59.[19]

The authors calculated kidney cancer risk based on these exposure categories in two ways. First, they compared Camp Pendleton marines to Camp Lejeune Marine with either "No/very low cumulative exposure" or "low to high cumulative exposure."[19] They did this to make sure that the increased kidney cancer risk was being caused by "cumulative exposures to the contaminants" rather than "due to some other factor."[19]

The results indicated that the kidney cancer risk was in fact due to the chemicals. For TCE, marines with No/Very low exposure (less than or equal to 1 microgram/liter-month) did not show an increased risk of kidney cancer (HR = 0.95, CI: 0.48-1.86). But for marines with low to high cumulative exposure (more than 1 microgram/liter-month), these marines had a 50% increased risk of kidney cancer compared to Camp Pendleton (HR =1.50, CI: 0.91-2.49).[19] Mr. Downs was exposed to a range of TCE in his water at Hadnot Point of 9-19 micrograms/liter monthly over a 20-month period of time and a range of TCE at Tarawa Terrace of 1.5-2.9 micrograms/liter monthly over a 20-month period of time.

For TVOC—which, again is a combination of all the chemicals—marines with No/Very low exposure (less than or equal to 1 microgram/liter-month) did not show an increased risk of kidney cancer (HR = 0.92, CI: 0.46-1.85).[19] But for marines with low to high cumulative exposure (more than 1 microgram/liter-month), these marines had a 50% increased risk of kidney cancer compared to Camp Pendleton (HR =1.50, CI: 0.91-2.47).[19] Mr. Downs was at an increased risk based on his monthly exposure.

The authors also calculated the risk based on exposure compared to marines with lower levels of exposure at Camp Lejeune. For TCE, marines with low, medium, and high exposures had risks of 1.54, 1.21, and 1.52, respectively.[19] For TVOC, marines with low, medium, and high exposures had risks of 1.42, 1.44, and 1.54, respectively.[19] The authors noted they "observed a monotonic exposure-response relationship for kidney cancer" and TVOC and a "non-monotonic exposure-response trend for PCE and kidney cancer."[19]

In sum, the results of Bove 2014a provide compelling evidence that exposure to Camp Lejeune water can cause kidney cancer. It also provides evidence that low levels of exposure to the relevant chemicals can cause kidney cancer.

Mr. Downs had an estimated level of exposure to contaminants in the Camp Lejeune water, in particular TCE and TVOC, that the data demonstrates is associated with the increased risks of kidney cancer shown above. For PCE, Mr. Downs exposure was in the highest category of all exposures and this category was shown to have significant increased risks of kidney cancer.

A second important report by Bove et al (Bove 2014b) compared civilians at Camp Lejeune to Civilians at Camp Pendleton.[20] The population of civilians at Camp Lejeune is similar to the population of Camp Pendleton. The stated purpose of the study was to answer one question of particular importance here: "to determine whether potential exposure of employees to contaminated drinking water at Camp Lejeune increased risk of mortality from cancers and other chronic diseases."[20]

Because "virtually all civilian workers at Camp Lejeune resided off-base," and thus "exposure to the contaminated drinking water would occur only when the civilians were at work at the base," this study provides particularly compelling evidence of the effect of even intermittent exposure to the CLJ water.[20] The risk ratio was 1.92 (0.58-6.34),[20] indicating that civilians at Camp Lejeune had a 92% higher risk of kidney cancer than those at Camp Pendleton—almost a doubling of the risk. This study again demonstrates that the chemicals at Camp Lejeune were present in sufficient quantities to cause kidney cancer. In particular, Mr. Downs lived and worked on base at Camp Lejeune for the entire time he was there. He would have had more daily exposure than individuals who resided off base.

A 2018 morbidity study was conducted by ATSDR and was based on a survey of more than 200,000 marines who were stationed at Camp Lejeune between 1972-1985 and a comparator group of 50,000 randomly selected marines who were stationed at Camp Pendleton during that same period.[21] The survey also included more than 8,000 civilians who were at Camp Lejeune and a comparator of over 7,000 civilians who were stationed at Camp Pendleton.[21] The purpose of the study was "to evaluate whether exposure to the contaminated drinking water at Camp Lejeune was associated with medically confirmed specific diseases of interest."[21] As compared to the marines at Camp Pendleton, the marines at Camp LeJeune had a relative of risk of kidney cancer of 1.31 (.86-1.99), corresponding to a 31% increased risk.[21] Civilians at Camp LeJeune had a relative risk of 1.52 (.69-3.35), corresponding to an increased risk of 52%.[21]

The authors performed analyses of kidney cancer risk based on exposure, comparing marines at Camp Pendelton to marines at Camp Lejeune with varying amounts of exposure to the specific chemicals in the water. These analyses used "water distribution system models" plus "residential locations and periods of residence at Camp Lejeune" to calculate "cumulative and average residential exposure to each contaminant."[21]

For marines at Camp Lejeune with medium exposure to TCE (defined as between 110 and 11,030 ppb-months), there was a relative risk of kidney cancer of 1.33 (.84-2.13), a 33% increased risk versus their peers at Camp Pendleton.[21] This corresponds with the estimated exposure for Mr. Downs to TCE, when his Hadnot Point exposure is factored into the analyses.

For civilians with medium TCE/PCE exposure (defined as between 10,868 and 50,563 ppb-months of TCE exposure or between 457 and 2118 ppb-months of PCE exposure), the relative risk was 1.80 (.68-4.76), corresponding to a 80% increased risk versus civilians at Camp Pendleton.[21] Again, this corresponds with the estimated exposure for Mr. Downs with regard to his PCE exposure.

The Bove 2024 study examined mortality by cancer type using a longer time horizon than in the previous studies. Again, the study compared personnel at Camp Lejeune to those at Camp Pendleton.[22] The study looked at personnel present at Camp Lejeune between 1972 and 1985.[22] The study showed that Navy/Marines personnel at Camp Lejeune had a hazard ratio of 1.21 (CI: 0.95-1.54) compared to personnel at Camp Pendleton, *i.e.*, a 21% increased risk.[22] The study authors also evaluated the risk of kidney cancer based on exposure, as measured by time spent on base. For marines/navy personnel on base, the authors found an increased risk of kidney cancer even at low duration, *i.e.*, 1-2 quarters on base—RR=1.33 (.95-1.86).[22]

A 2024 update by Bove et al found an adjusted hazard ratio of 1.06 (0.95, 1.18) for kidney cancer incidence in marines in Camp Lejeune relative to those who served in Camp Pendleton.[23] Civilians in this study were found to have a higher HR of 1.12.[23]

The Camp Lejeune epidemiology provides the best and most compelling evidence of the levels that are sufficient to cause kidney cancer, however, other epidemiology studies in different contexts provide relevant information as well. There are a number of additional levels seen in the literature relating to TCE and the other chemicals, such as PCE, that have been found to be causally associated to kidney cancer. These have been detailed in the General Causation reports of Drs. Hatten and Bird that I have reviewed. Mr. Downs would have met many of these levels as well, including his TCE, PCE and VC exposures. These reports inform my analysis in this case and support my opinions.

I have concluded that the water at Camp Lejeune was contaminated with significant levels of trichloroethylene (TCE) and other volatile organic compounds including perchloroethylene (PCE) and vinyl chloride (VC). Based upon the extended duration of time Mr. Downs was at Camp Lejeune, the very significantly elevated levels of the chemicals in the water and the frequency with which Mr. Downs came into contact with the toxins at issue, primarily TCE, it is reasonable to conclude Mr. Downs' exposure was substantial and not de minimis. There is scientific evidence to support causality of each toxin to kidney cancer, using the at least as likely as not standard or equipoise.

One can conclude to a reasonable degree of medical and scientific certainty, based on these studies and the case history of David Downs, that exposure to carcinogens at Camp Lejeune, primarily TCE, was "more likely than not" the cause of his kidney cancer. Also, the above evidence provides an adequate and valid basis for including the contaminated water at Camp Lejeune as a cause of Mr. Downs' kidney cancer.

IX. ATSDR/Bove Data on the Levels of the Chemicals in the Water

The ATSDR stated the following in its report regarding the contaminated water at issue,

> "The Hadnot Point treatment plant provided drinking water to the main portion of the base at Camp Lejeune, including most of the barracks and workplaces. Samples of the Hadnot Point distribution system were conducted by the base in May and July 1982, December 1984, and throughout 1985. During the 1982 sampling, measured levels of TCE and PCE in the distribution system of Hadnot Point were as high as 1,400 ppb and 100 ppb, respectively. Vinyl chloride and benzene were also detected in the Hadnot Point distribution system during sampling conducted on or after December 1984. The Tarawa Terrace treatment plant provided drinking water to the Tarawa Terrace housing area at the base. Samples of the Tarawa Terrace distribution system were conducted by the base in May and July 1982, and February 1985 onward. During the July 1982 distribution system sampling, PCE was measured as high as 104 ppb and reached a maximum of 215 ppb during the February 1985 sampling. The current U.S. maximum contaminant levels (MCLs) for TCE and PCE are 5 ppb. The MCLs for vinyl chloride and benzene are 2 ppb

> and 5 ppb, respectively. The MCLs for TCE, vinyl chloride and benzene were in effect as of 1989, and the MCL for PCE was in effect as of 1992. Historical reconstruction modeling of the drinking water contamination indicated that TCE and PCE levels above their current MCLs were likely present in the distribution systems since the 1950s. The highly contaminated supply wells serving these systems were shut down by February 1985. For the retrospective cohort study of Marines and Navy personnel at Camp Lejeune, the relevant exposure period was 1975 – January 1985. The estimated monthly average contaminant concentrations in the Hadnot Point and Tarawa Terrace systems during this period are shown in tables in the appendix of this report. In the Hadnot Point system, the median monthly estimated average concentrations of TCE, PCE, vinyl chloride and benzene was 366 ppb, 15 ppb, 22 ppb and 5 ppb, respectively. In the Tarawa Terrace system, the median monthly estimated average concentrations of PCE, TCE and vinyl chloride were 85 ppb, 4 ppb and 6 ppb. The median number of months a marine or Navy personnel was stationed at the base was 18 months."[2]

I have also reviewed the levels of the toxins in the water from the water modeling reports that were done by ATSDR and Plaintiff's expert Morris Maslia, which showed significant and substantial levels of the toxins at issue in the water at Camp Lejeune during the time Mr. Downs was present.

X. David Downs' Exposure

David Downs served at Camp Lejeune from 2/1960 to 9/1961 and was located both at Hadnot Point and Tarawa Terrace. Mr. Downs lived at Tarawa Terrace and worked at Hadnot Point. This resulted in exposure to both TCE at Hadnot Point and trichloroethylene (TCE), tetrachloroethylene (PCE), 1,2-dichloroethylene (DCE) and vinyl chloride at Tarawa Terrace.

According to ATSDR, a marine in training at Camp Lejeune consumes an estimated 6 liters of water per day for three days per week and 3 liters per day the rest of the week.[2] Under warm weather conditions, a marine may consume between 1 and 2 quarts of water per hour and shower twice a day.[19] According to the ATSDR, it is likely that during training, the water supplied in the field came from the Hadnot Point water system with both measured and estimated levels of TCE and PCE substantially higher than their MCLs.[2]

During Mr. Downs approximately 589 days of exposure at Camp Lejeune, he had exposures to approximately 43 microgram/liter TCE, 939 microgram/liter PCE and 122 microgram/liter vinyl chloride at Tarawa Terrace. He was exposed to approximately 282 microgram/liter TCE at Hadnot Point. Mr. Downs was exposed to the following specific levels of chemicals at Tarawa Terrance:

strong associations with the development of non-Hodgkin's lymphoma, multiple myeloma, and KC.[1] Owing to its lipophilic nature, TCE rapidly accumulates in the kidney, where it can be metabolized to cysteine-S-conjugates, the metabolites thought to be responsible for the carcinogenic effects. Prolonged exposure to TCE is associated with a significant increase in the risk of KC development (odds ratio 1.78, 95% CI 1.05–3.03) and mortality.[30] A recent epigenome-wide association study in TCE-exposed workers highlighted elevated genome-wide DNA methylation variation and differential expression of genes involved in cell matrix adhesion and interferon subtypes, known to be related to cancer development.[31]

XII. TCE and Kidney Cancer Outside of Camp Lejeune

Strong evidence exists outside of Camp Lejeune for the carcinogenesis of TCE with respect to kidney cancer.[1,2,6,7,8,10,15,16,32,33,34] Epidemiologic research has centered upon workers most heavily exposed through occupational degreasing of metals and other materials. One exemplary case-control study, Charbotel et al., evaluated the effect of TCE on kidney cancer in 86 affected cases and 316 controls in a geography with high occupational exposure to cutting fluids.[32] The authors utilized a job-task exposure matrix (JTEM) to establish cumulative exposure to TCE.[32] A significant relationship was found with an OR 2.16 (95% CI, 1.02–4.60) when accounting for tobacco smoking and BMI.[32] The study strengthened the argument for a causal association by also demonstrating a significant dose-response relationship (p=0.04).[32]

The evidence provided by individual studies is strengthened by several metanalyses and systematic reviews on the topic. Scott et al. in conjunction with the Environmental Protection Agency (EPA) carried out a systematic review on the effect of TCE upon kidney cancer.[9] This review comprised 15 cohort and case-control studies specific to kidney cancer.[9] The reported summary relative risk (RR) was 1.27 (95% CI 1.13-1.43) for overall TCE exposure and kidney cancer risk.[9] Of note, a highest risk group was compiled from all studies with a preference toward quantification of cumulative exposure, though often only duration of exposure was reported. The RR for the highest exposure group was 1.58 (95% CI: 1.28-1.96).[9] Lack of sensitivity to alternative risk estimate selections and removal of individual studies added to the robust nature of this study. Although tobacco exposure was not quantified in all included studies, the RR for lung cancer among those exposed was not significantly increased.[9] Karami et al. performed a meta-analysis with similar findings.[8] Though composed largely by studies overlapping with those evaluated by Scott et al., several new publications were included.[8]

Meta-analyses that have been conducted have observed an elevated summary RR in the 1.3-1.4 range and that higher cumulative exposures increased the risk of kidney cancer.[2,9,33] The meta-analyses conducted by Scott and Jinot 2011 and Karami et al. 2012 reported no between-study heterogeneity or evidence of publication bias.[2,9,33] Scott and Jinot 2011 concluded that confounding by smoking and other risk factors would have a minimal impact on the kidney cancer meta-analysis results.[2,9] NTP (2015) in its Monograph on Trichloroethylene conclude that the increased risks found in the majority of epidemiological studies were unlikely to be explained by selection biases.[2,6] IARC (2014) and EPA (2011) concluded that there is sufficient human evidence that TCE causes kidney cancer.[1,2,5] The NTP concluded: "Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk across studies with different study designs, in different

geographical areas, and in different settings; evidence of increasing cancer risk with increasing level or duration of exposure; and meta-analyses showing statistically significantly increased cancer risk across studies."[2,6] NTP (2015) further noted that the increased risk of kidney cancer was found among individuals with the higher levels of exposure and in studies with better assessments of exposure and disease.[2,6]

Several other studies have investigated the relationship between TCE and kidney cancer with varying results. Hansen et al. 2013 had a good study design due to its large pool cohort, evaluation of cancer incidence, documented TCE exposure, minimal cofounding, and an analysis of exposure-response trend.[2]. This study observed an elevated risk among those with the highest levels of urine TCA (RR=2.04; 95% CI: 0.81, 5.17).[2,10] The study was limited because exposure levels among most workers were low.[2,10] The study also relied on only a few urine TCA measurements to assess exposures and there were a small number of exposed cases in the exposure-response analysis.[2,10] Two other studies did not observe an increased risk for kidney cancer.[2,11,12] However, Vlaanderen et al. 2013 had severe limitations because it only had a small population who received high exposure and used a generic JEM which was likely to introduce considerable exposure misclassification.[2,11] The Christensen et al. study was also severely limited due to few exposed cases.[2,12] Four other studies including Silver et al. 2014, Buhagen et al. 2016, and the two Camp Lejeune studies, Bove et al. 2014 a, b, observed increased risks of kidney cancer.[2,13,14,19,20]

One study of particular importance is Moore et al. 2010 because it not only evaluates exposure-response trends but also the interaction between TCE exposure and genotypes for the GSTT1 and renal-CCBL1enzymes.[2,15] These enzymes are highly active in the kidney and involved in the bioactivation of TCE (via GSH-conjugation pathway).[2,15] NTP (2015) and ATSDR (2017) both considered Moore et al. 2010 of high utility.[2,6] Moore et al. 2010 found an exposure-response trends for TCE exposure and kidney cancer[2,15] The study also found that those exposed to TCE with at least one intact GSTT1 allele had elevated risks for kidney cancer, but those with a functionally inactive GSTT1 enzyme (i.e., with two deleted alleles, the null genotype) had **no elevated risk**.[2,15] Based on the interaction between TCE exposure and minor alleles for the renal-CCBL1 enzyme, the study supported the findings for the GSTT1 enzyme and the hypothesized mechanism for TCE-induced kidney cancer.[2,15] Moore et al. therefore provides strong evidence for causality.[2,15]

There is also body of literature identifying the likely mode of action for trichloroethylene-induced kidney cancer based on animal studies and mechanistic information. The available data provides support for a mutagenic and cytotoxic mode of action mediated by GSH-conjugation-derived metabolites.[2] "There is experimental evidence that GSH metabolites (particularly DCVC) are genotoxic and nephrotoxic and are both formed in and delivered to the kidney following exposure to trichloroethylene."[2,6] Exposure to TCE via inhalation or stomach tube has been observed to cause kidney cancer in rats.[2,5]

Moore et al. 2010 and Raaschou-Nielsen 2003 found increased risk of kidney cancer with increasing duration of exposure to TCE.[2,15,16] The Moore et al. 2010 study also suggested that an elevated risk could occur with a short duration of exposure (OR=1.22, 95% CI: 0.48, 3.12 for <1,080 hours exposure duration).[2,15] Scott and Jinot 2011 and Kelsh et al. 2010 found an

increased risk with higher cumulative exposures.[2,9,34] Bove et al. 2014a observed a monotonic trend for kidney cancer and cumulative exposure for TVOC at Camp Lejeune but not for TCE or the other contaminants when analyzed separately.[2,19]

XIII. TCE Mechanism of Injury

Trichloroethylene (TCE) is a volatile organic compound that was widely used in industrial settings. Multiple lines of evidence support a link between TCE exposure and cancer, particularly kidney cancer [1] TCE produces other toxic effects including neurotoxicity, immunotoxicity, developmental cardiac toxicity, kidney toxicity, liver toxicity, and male reproductive toxicity.[35]

One mechanism of toxicity of TCE is through alterations of DNA methylation.[36] This commonly studied epigenetic mark involves the addition of a methyl group to cytosine that is adjacent to a guanine (a CpG) site. DNA methylation modulates transcription by altering accessibility of proteins to DNA and it is a key regulator of a number of important processes such as aging, disease, and development.[37] DNA methylation has also become increasingly recognized as a mediator of toxicity of environmental chemical exposures.[36]

TCE induces epigenetic aberrations in various studies in cell lines and animal models.[31] Human exposure to trichloroethylene is associated with increased variability of blood DNA methylation that is enriched in genes and pathways related to autoimmune disease and cancer.[31] To evaluate associations between TCE exposure and DNA methylation in humans, Phillips et al. conducted an epigenome-wide association study (EWAS) in TCE exposed workers using the HumanMethylation450 BeadChip.[31] They investigated differences in mean DNA methylation and differences in variability of DNA methylation between 73 control (< 0.005 ppm TCE), 30 lower exposed (< 10 ppm TCE), and 37 higher exposed (greater than or equal to 10 ppm TCE) subjects' white blood cells.[31] They found that TCE exposure increased methylation variation globally (Kruskal-Wallis p-value = 3.75e-3) and in 25 CpG sites at a genome-wide significance level (Bonferroni p-value < 0.05).[31] Human exposure to TCE "was associated with epigenetic alterations in genes involved in cell-matrix adhesions and interferon subtype expression, which are important in the development of autoimmune diseases; and in genes related to cancer development."[31] These results suggest that DNA methylation may play a role in the pathogenesis of TCE exposure-related diseases and that TCE exposure may contribute to epigenetic drift.

The following is a table from ATSDR detailing some of the studies referenced above and that are relevant to this overall analysis:

Kidney Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Kelsh 2010 **meta-analysis**	TCE	Not reported	sRR=1.42 (1.13, 1.77) – 23 studies; "More likely exposed": sRR=1.34 (1.07, 1.67) – 8 cohort studies	"Shortest" duration: RR=1.50 (0.96, 2.36) – 7 studies "Longest" duration: RR=1.24 (0.69, 2.23) – 7 studies	"Low" cumulative exposure: RR=1.29 (0.68, 2.47) – 3 studies "High" cumulative exposure: RR=1.39 (0.75, 2.59) – 3 studies
Scott 2011, EPA **meta-analysis**	TCE	Not reported	sRR=1.27 (1.13, 1.43) – 15 studies; (11 incidence (I), 4 mortality M))	–	High cumulative exposure, summary RR=1.64 (1.31, 2.04) – 10 studies
Karami 2012 **meta-analysis**	TCE	478 (?)**	sRR=1.32 (1.17, 1.50) – 18 studies (9 cohort – 4 I, 5 M; 9 case-control – 8 I, 1 M)	–	–
Cohort Studies:					
Anttila 1995+ ⊕ Incidence 849 1967-1992	PCE (blood PCE)	2	SIR=1.82 (0.22, 6.56)		
Raaschou-Nielsen 2003 + Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data)	76		Duration of employment (yr) (SIR) # cases Men Women <1: 0.8 (0.5, 1.4) 14 1.1 (0.1, 3.8) 2 1-4.9: 1.2 (0.8, 1.7) 25 1.2 (0.2, 3.4) 3 ≥5: 1.6 (1.1, 2.3) 29 1.5 (0.3, 4.3) 3	
Zhao 2005¶ Incidence 5,049 1988-2000 **NTP: High Utility**	Aerospace TCE (JEM)	6 4			Cumulative Exposure (RR) Med: 1.9 (0.6, 5.2) High: 4.9 (1.2, 19.6)
Radican 2008+ Mortality 10,730 men¥ 1953-2000 **NTP: Moderate Utility**	Aircraft maintenance TCE (walk-through surveys, interviews, job tasks, air monitoring data)	16		Cumulative Exposure (unit-yr) HR 0-5: 1.9 (0.6, 6.0) – 10 cases 5-25: 0.3 (0.0, 2.8) – 1 case >25: 1.2 (0.3, 4.3) – 5 cases	Exposure intensity (HR) # cases Low, intermittent: 1.6 (0.5, 4.8) 15 Low, continuous: 1.8 (0.6, 5.6) 11 Peak, infrequent: 1.0 (0.2, 5.7) 2 Peak, frequent: 1.1 (0.3, 4.0) 6

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Lipworth 2011+++ Mortality 5,830 (PCE) 1960-2008	Aircraft Manufacturing PCE (JEM)	13	Any exposure: SMR=0.80 (0.43, 1.37)	Duration of exposure (yr) (RR) # cases TCE PCE <1: 0.84 (0.48, 1.47) 18 1.26 (0.65, 2.45) 11 1-4: 1.10 (0.59, 2.04) 14 1.00 (0.50, 2.00) 10 ≥5: 1.02 (0.55, 1.90) 15 1.02 (0.53, 1.99) 12	
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008 **NTP: Moderate Utility**	TCE (urine TCA)	32 19	SIR=1.01 (0.70, 1.42) 20 yr lag: SIR=1.11 (0.67, 1.73)		Urine TCA (mg/L): (RR) <5: referent 5-25: 1.1 (0.5, 2.7) – 11 cases 25-50: 0.8 (0.2, 3.0) – 3 cases >50: 2.0 (0.8, 5.2) – 9 cases
Silver 2014 Mortality 34,494 1969-2009	Microelectronics firm TCE (JEM) PCE (JEM) •	56			Cumulative exposure (5 exposure-yr) HR=1.24 (0.87, 1.77) HR=0.15 (0.01, 4.04)
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	13	SIR=1.7 (1.0, 3.0)		
Case-Control Studies:					
Pesch 2000+ Incidence 935 cases 4,298 controls	Questionnaire and JTEM TCE PCE	M F 68 11 59 7 22 5 44 8 39 6 15 3		Cumulative exposure (percentiles) Odds ratios Males: Females 30th: 1.3 (1.0, 1.8) 1.3 (0.7, 2.6) 60th: 1.1 (0.8, 1.5) 0.8 (0.4, 1.9) 90th: 1.3 (0.8, 2.1) 1.8 (0.6, 5.0) 30th: 1.2 (0.9, 1.7) 2.2 (0.9, 5.2) 60th: 1.1 (0.7, 1.5) 1.5 (0.6, 3.8) 90th: 1.3 (0.7, 2.3) 2.0 (0.5, 7.8)	
Charbotel 2006+ Incidence 86 cases 316 controls **NTP: High Utility**	TCE (occupational questionnaire & JTEM)	37	Ever exposed, OR=1.64 (0.95, 2.84)		Cumulative dose: (ORs) Low: 1.6 (0.8, 3.5) – 12 cases Med: 1.2 (0.5, 2.8) – 9 cases High: 2.2 (1.0, 4.6) - 16 cases

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Moore 2010** Incidence 1,097 cases 1,476 controls **NTP: High Utility**	TCE (occupational questionnaire & JTEM)	29	High confidence, any exposure: OR=2.05 (1.13, 3.73)	<1,080 hours, OR=1.22 (0.48, 3.12) – 9 cases; ≥1,080 hours, OR=2.86 (1.31, 6.23) – 20 cases	<1.6 ppm-years: OR=1.77 (0.64, 4.80) – 9 cases; ≥1.6 ppm-years: OR=2.23 (1.07, 4.64) – 20 cases <0.076 ppm intensity: OR=1.73 (0.75, 4.02) – 13 cases; ≥0.076 ppm intensity: OR=2.41 (1.05, 5.56) – 16 cases
Vlaanderen 2013 Incidence 76,130 cases 380,650 controls 1961-2005	TCE (JEM) PCE (JEM) Benzene (JEM)	 1,217 1,556 1,372 375 333 314 1359 1435 1560	Tertiles of cumulative exposure: 1. HR=1.01 (0.95, 1.07) 2. HR=1.02 (0.97, 1.08) 3. HR=1.00 (0.95, 1.07) 1. HR=1.11 (0.99, 1.24) 2. HR=0.96 (0.86, 1.08) 3. HR=0.94 (0.83, 1.06) 1. HR=1.00 (0.94, 1.06) 2. HR=1.00 (0.95, 1.06) 3. HR=1.06 (1.00, 1.12)		>90th percentile cumulative exposure: (HRs) TCE: 0.86 (0.75, 0.98) 251 cases PCE: 0.81 (0.65, 1.01) 88 cases >90th percentile, intensity x freq. exp. TCE: 1.00 (0.90, 1.30) 387 cases PCE: 1.01 (0.82, 1.25) 103 cases
Christensen 2013# Incidence 177 cases 533 controls	TCE PCE	5 2 2 2	Any exposure: OR=1.0 (0.3, 2.9) "substantial": OR=0.7 (0.1, 3.2) Any exposure: OR=1.6 (0.3, 9.4) "substantial": OR=3.1 (0.4, 24)	–	–
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry Cleaning	8	SMR=1.0 (0.4, 2.0)		Exposure intensity # cases Little/no: SMR=0.3 (0.0, 1.6) 1 Med/high: SMR=1.5 (0.6, 3.1) 7
Lynge 2006 Incidence 158 cases 785 controls 1970-2001	Dry Cleaning	29	RR=0.67 (0.43, 1.05)		

XIV. Bradford Hill Analysis of Causation for David Downs

To make this analysis more robust, I have looked at the Bradford Hill factors to make a determination as to what weight to give the causal association between the water at Camp Lejeune and Mr. Downs' kidney cancer.[17]

An association between TCE exposure and kidney cancer has been identified in multiple studies involving occupational exposures and Camp Lejeune water system exposures. The following discussion evaluates the evidence in order to determine whether it is "more likely than not" that this demonstrated association is the cause of Mr. Downs' kidney cancer.

Strength of Association: Many studies demonstrate elevated measures of association between TCE and kidney cancer.[14,15,16,19,21,32,38,39,40,41,42,43,44,45,46,47] These range up to an OR of 10.8.[45] Similarly, multiple meta-analyses have identified an elevated measures of association ranging from RR 1.27 to RR 1.42, providing a realistic estimate of the true population risk of kidney cancer following exposure to TCE.[9,33,34] This body of literature provides strong evidence that exposure to TCE is a cause of kidney cancer given the demonstrated strength of association in the epidemiologic literature.

Mr. Downs was stationed at Camp Lejeune between February 1960 and September 1961 and was exposed to PCE, TCE and VC at Hadnot Point and Tarawa Terrace. He had no other potential causes of kidney cancer that one would consider as likely as this environmental exposure, such as a significant family history or significant smoking history.

Consistency: The literature is comprehensive and consistent in demonstrating that TCE is a cause of kidney cancer among other cancers. There are both individual studies of largely inhalational occupational exposures[11,14,15,16,32,38,39,40,41,42,43,44,45,46,47] and water system contamination[19,20,21,30] that demonstrate a consistent association in different populations between TCE and kidney cancer. These also identify different routes of exposure which all result in exposure to TCE being associated with kidney cancer. This association is also consistent whether analyzing kidney cancer diagnosis[11,14,15,16,21,32,41,42,43,45,47] and kidney cancer mortality.[19,20,38,39,40,42,44,46]

Furthermore, cohort studies[11,14,1619,20,38,39,40,42,44,46,47] and case-control studies[15,21,32,41,43,45] reach nearly identical conclusions.

There are similar conclusions in meta-analyses (Hansen 2013; Karami 2012; Kelsh 2010; Scott 2011).[9,10,33,34] Since Mr. Downs was exposed to TCE and the other chemicals through a variety of routes (ingestion, inhalation and dermal) these studies all support this as a cause of his kidney cancer.

Exposure-Response: There are studies that support a monotonic exposure-response for increased intensity of TCE exposure with increased kidney cancer .[15,21,32,34,45,47] Even subjects of low exposure were at higher risk for developing kidney cancer.

Temporality: Multiple studies utilized prolonged lags to ensure that exposure to TCE occurred sufficiently far before the identification of a kidney cancer case to be a cause of that outcome of interest.[10,11,15,16,19,20,30,40,43,44,47,48] Other studies reported prolonged latency periods or follow up times.[42,45,49] Such study designs provide evidence for causation that accounts for the principle of **temporality**, that the exposure of interest must occur sufficiently prior to the outcome of interest to be a possible cause.

[redacted] This would be consistent with a sufficient lag time to develop cancer from a carcinogenic exposure.

Biological Plausibility: Exposure to TCE follows a clear biologically plausible pathway for causation on kidney cancer. As discussed previously, TCE induces epigenetic aberrations in various studies in cell lines and animal models.[50,51,52,53] This provides clear support for a **biologically plausible** pathway from TCE exposure to development of kidney cancer.

Analogy: Trichloroethylene (TCE) is a volatile organic compound that was widely used in industrial settings. Multiple lines of evidence support a link between TCE exposure and cancer, particularly kidney cancer, which led the International Agency for Research on Cancer (IARC) to classify TCE as a Group 1 carcinogen.[1] TCE also produces other toxic effects including neurotoxicity, immunotoxicity, developmental cardiac toxicity, kidney toxicity, liver toxicity, and male reproductive toxicity.[35] There are other organic compounds, such as PCE, that are also carcinogenic in similar ways.[1]

Mr. Downs was exposed to TCE as well as PCE and vinyl chloride. TCE is so clearly related to kidney cancer that it is likely the primary causal agent for Mr. Downs. However, the other chemicals he was exposed to likely contributed to his kidney cancer either additively or synergistically.

Experiment: There is no human **experimental** evidence of causation involving TCE and kidney cancer because it is unethical. However, there is as noted a vast amount of evidence from individual studies and meta-analyses that support the association of TCE and kidney cancer as well as data from military personnel and civilians stationed at Camp Lejeune when compared to those who served in camp Pendleton.[19,20,21,22,23]

Specificity: There is evidence that TCE exposure is a cause of many cancers but not all cancers. There is strong evidence noted above that it is a cause of kidney cancer which is the cancer that Mr. Downs developed.

Coherence: The human, animal, and mechanistic literature provides a robust and **coherent** body of evidence for TCE exposure as a cause of kidney cancer. There is no substantial contrary data suggesting an alternative explanation for the observed measures of association. Similarly, Mr. Downs had clear exposure to TCE and other chemicals at Camp Lejeune and there is a lack of other strong risk factors for his kidney cancer.

XV. Differential Diagnosis of Etiology

In determining the potential causes of the kidney cancer Mr. Downs developed, I weighed the possible risk factors for the disease. [redacted]

His main carcinogenic exposure was to carcinogens, such as TCE, at Camp Lejeune. The evidence that TCE is a causative agent for kidney cancer is conclusive. His exposure to the other chemicals such as PCE and VC also likely contributed to his kidney cancer, either additively or synergistically. These chemicals are also known carcinogens. Mr. Downs' exposure to PCE was labeled by Bove and ATSDR to be in the highest exposure categories.

[redacted]